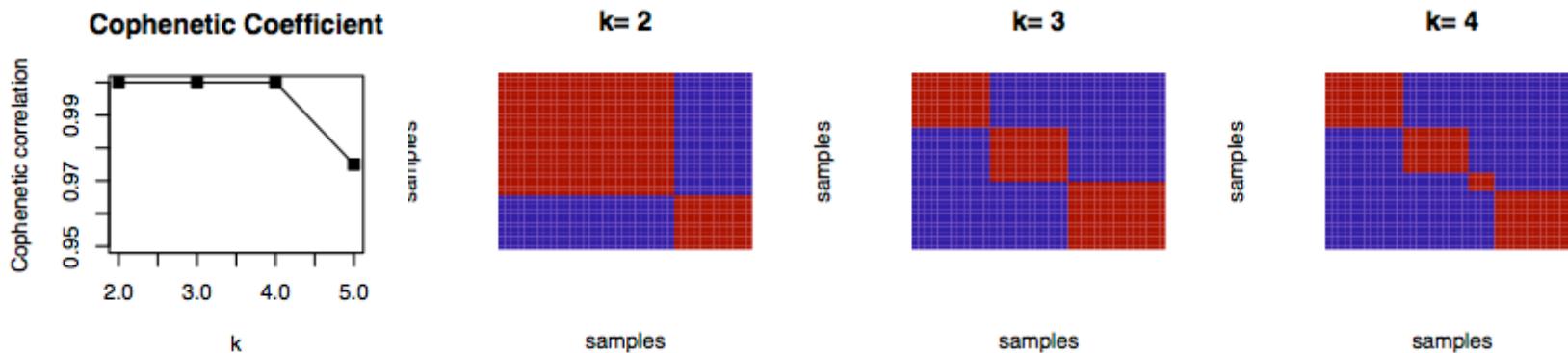
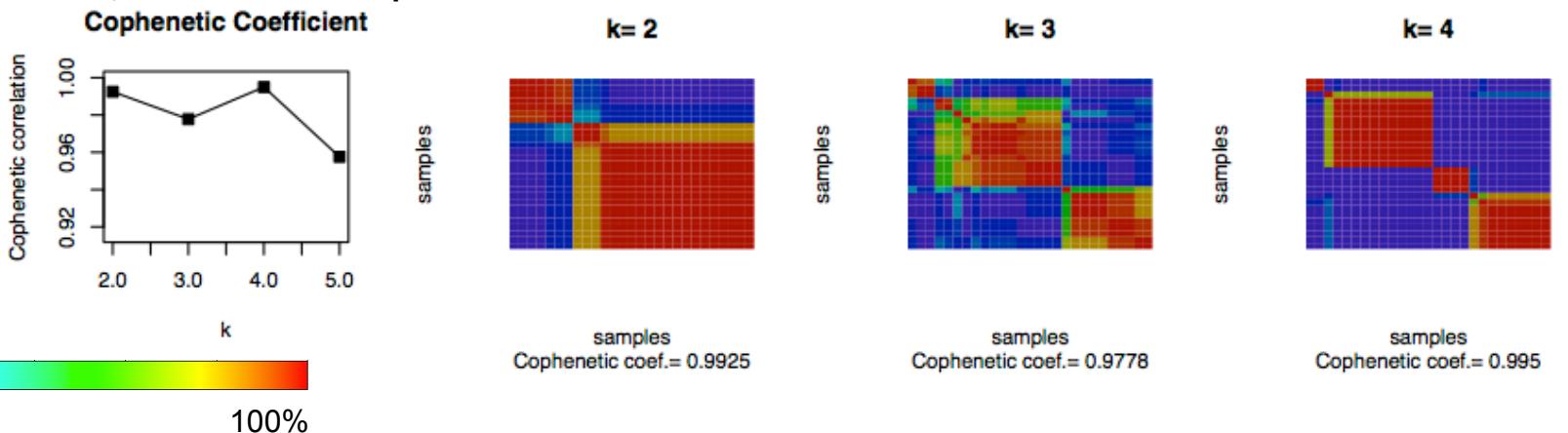


Supplementary Figure 1. NMF analysis of core clinical microarray datasets after selecting for genes with $SD \geq 0.8$

a: NMF, Badea et al., Tumor Samples



b: NMF, UCSF Tumor Samples

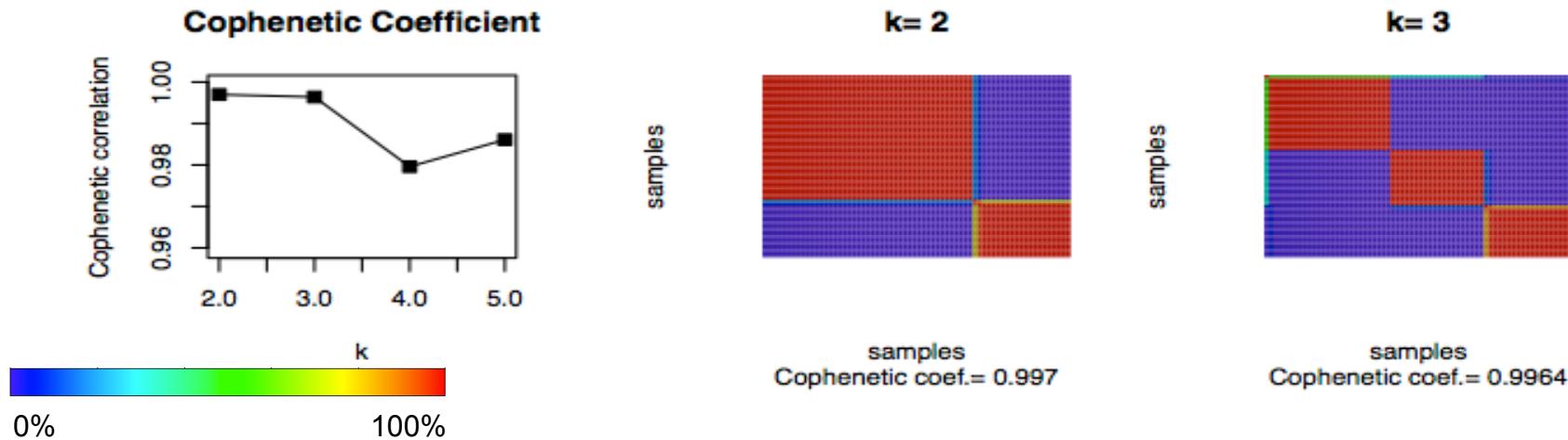


1a. NMF analysis of Badea et al. microarray dataset after selecting for genes with SD greater than 0.8. Maximum cophenetic coefficient occurred for $k = 2$ to 4 clusters. Consensus matrix (right panel) for $k = 2$ to 4 are shown.

1b. NMF analysis of the UCSF PDA microarray dataset after selecting for genes with SD greater than 0.8. Maximum cophenetic coefficient occurred for $k = 2$ to 4 clusters. Consensus matrix (right panel) for $k = 2$ to 4 are shown.

Supplementary Figure 2. NMF analysis of merged microarray datasets

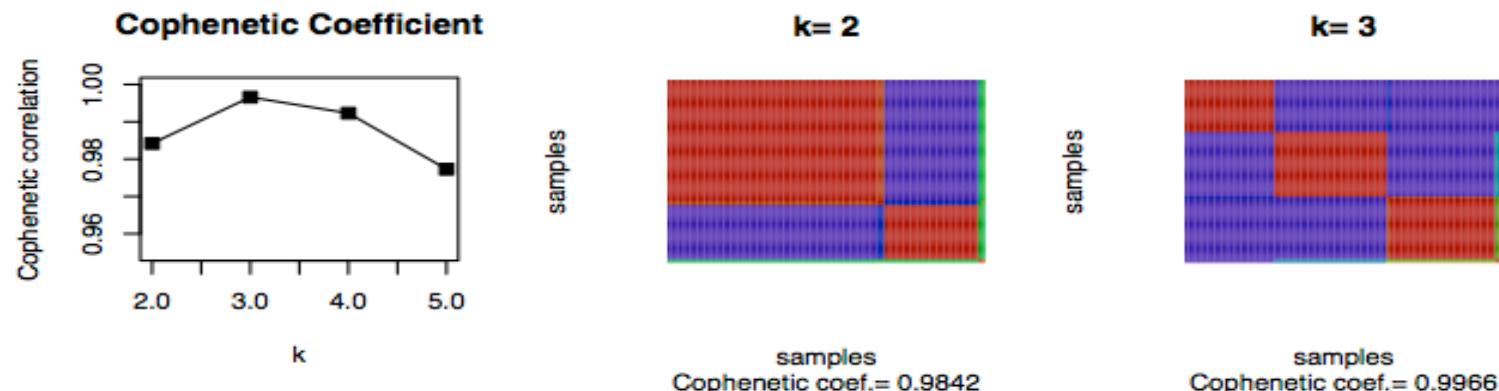
a: NMF, Merged UCSF and Badea et al., Tumor Samples



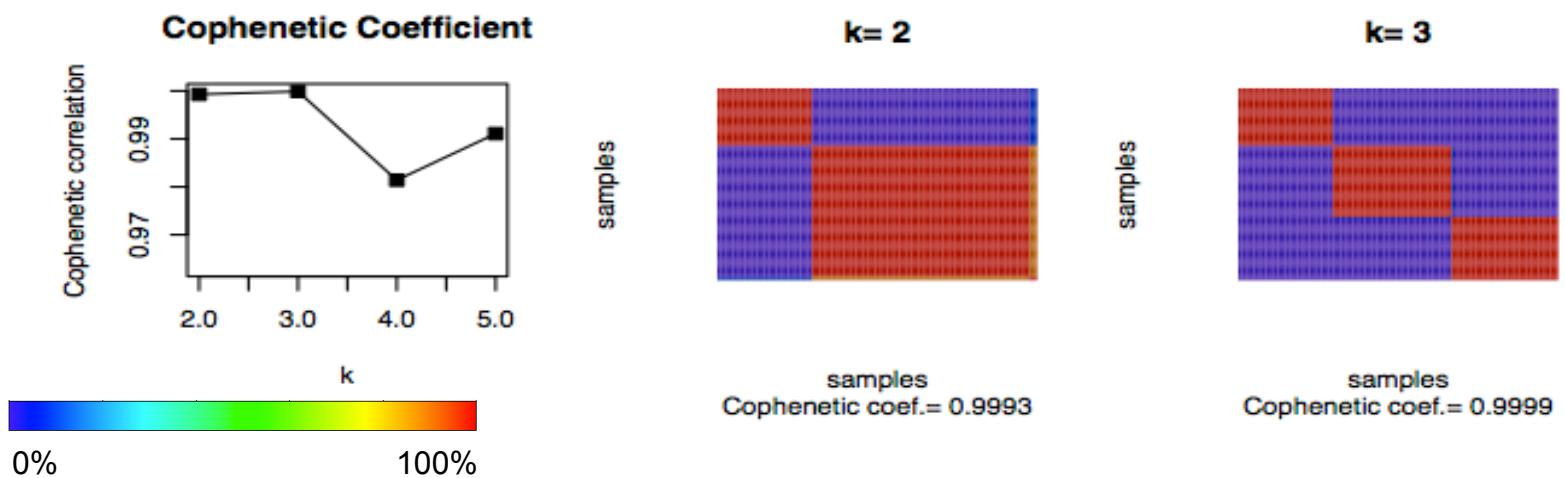
2a. NMF analysis of DWD merged UCSF and Badea et al. (i.e. core clinical) PDA microarray datasets using common probes with SD greater than 0.8. Maximum cophenetic coefficient occurred for k = 2 to 3 clusters. Consensus matrix (right panel) for k = 2 and 3 are shown.

Supplementary Figure 2

b: NMF, Merged Core Tumor Samples and Human Cell Line Microarray Dataset



c: NMF, Merged Core Tumor Samples and Mouse Cell Line Microarray Dataset

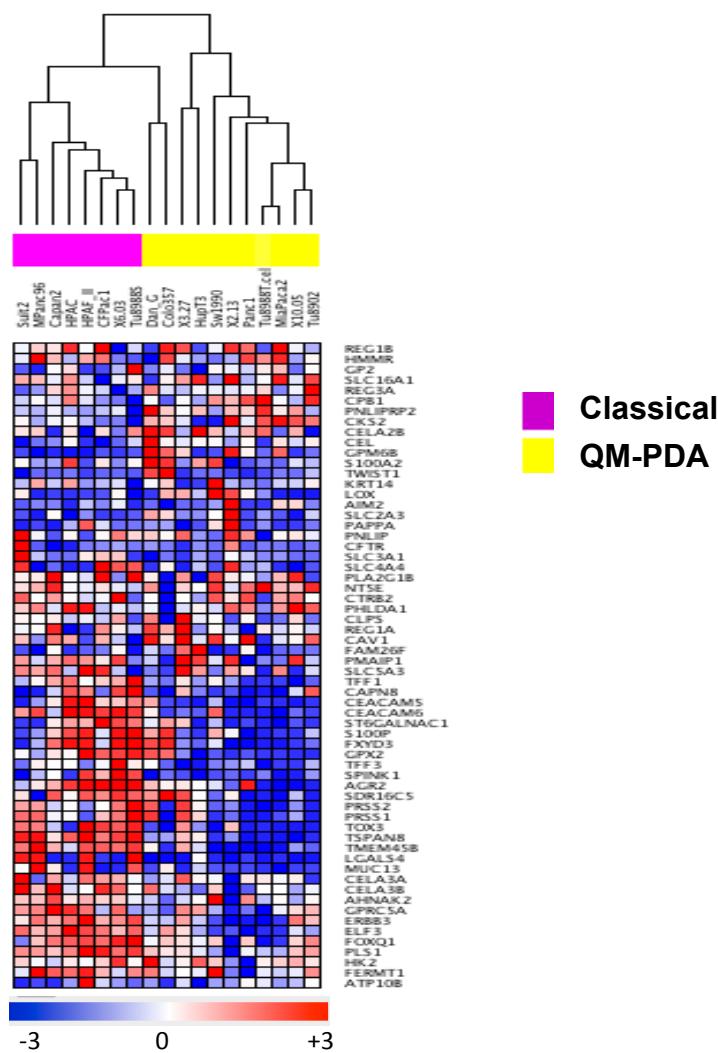


2b. NMF analysis of DWD merged core clinical PDA datasets with human PDA cell line microarray dataset using *PDAssigner* genes. Maximum cophenetic coefficient occurred for k = 2 to 4 clusters. Consensus matrix (right panel) for k = 2 and 3 are shown.

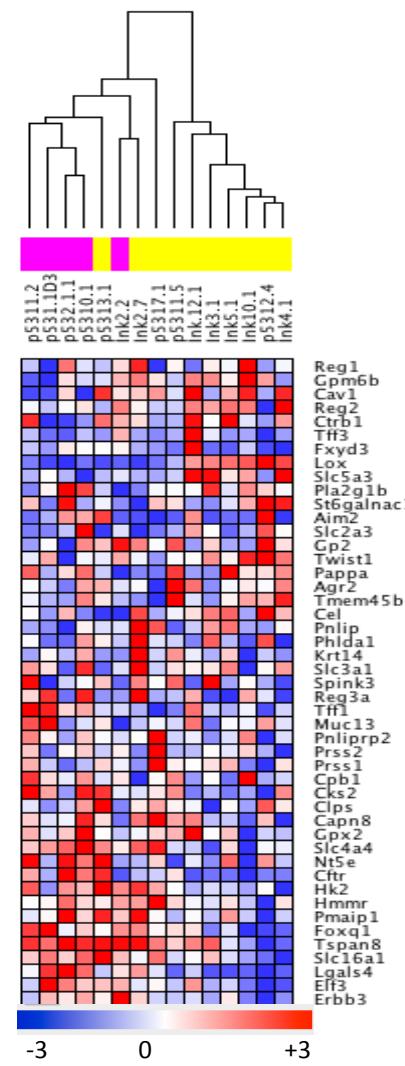
2c. NMF analysis of DWD merged core clinical PDA dataset with mouse PDA cell line microarray dataset using *PDAssigner* genes. Maximum cophenetic coefficient occurred for k = 2 to 3 clusters. Consensus matrix (right panel) for k = 2 and 3 are shown.

Supplementary Figure 2

d: PDAssigner Genes from Human Cell lines



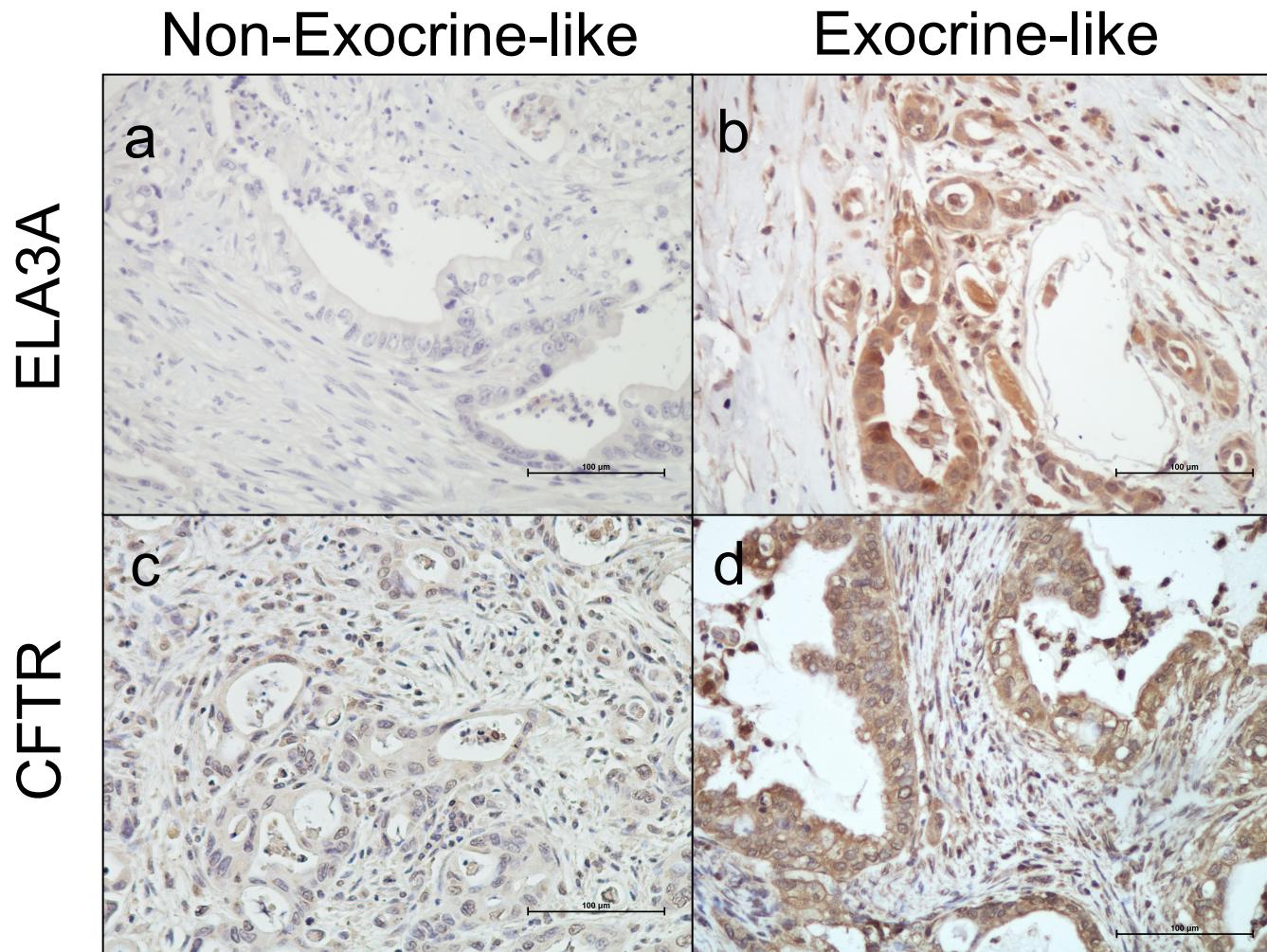
e: PDAssigner Genes from Mouse Cell lines



2d. Hierarchical clustering of human PDA cell lines with PDAssigner genes. The clusters show classical and QM-PDA subtypes.

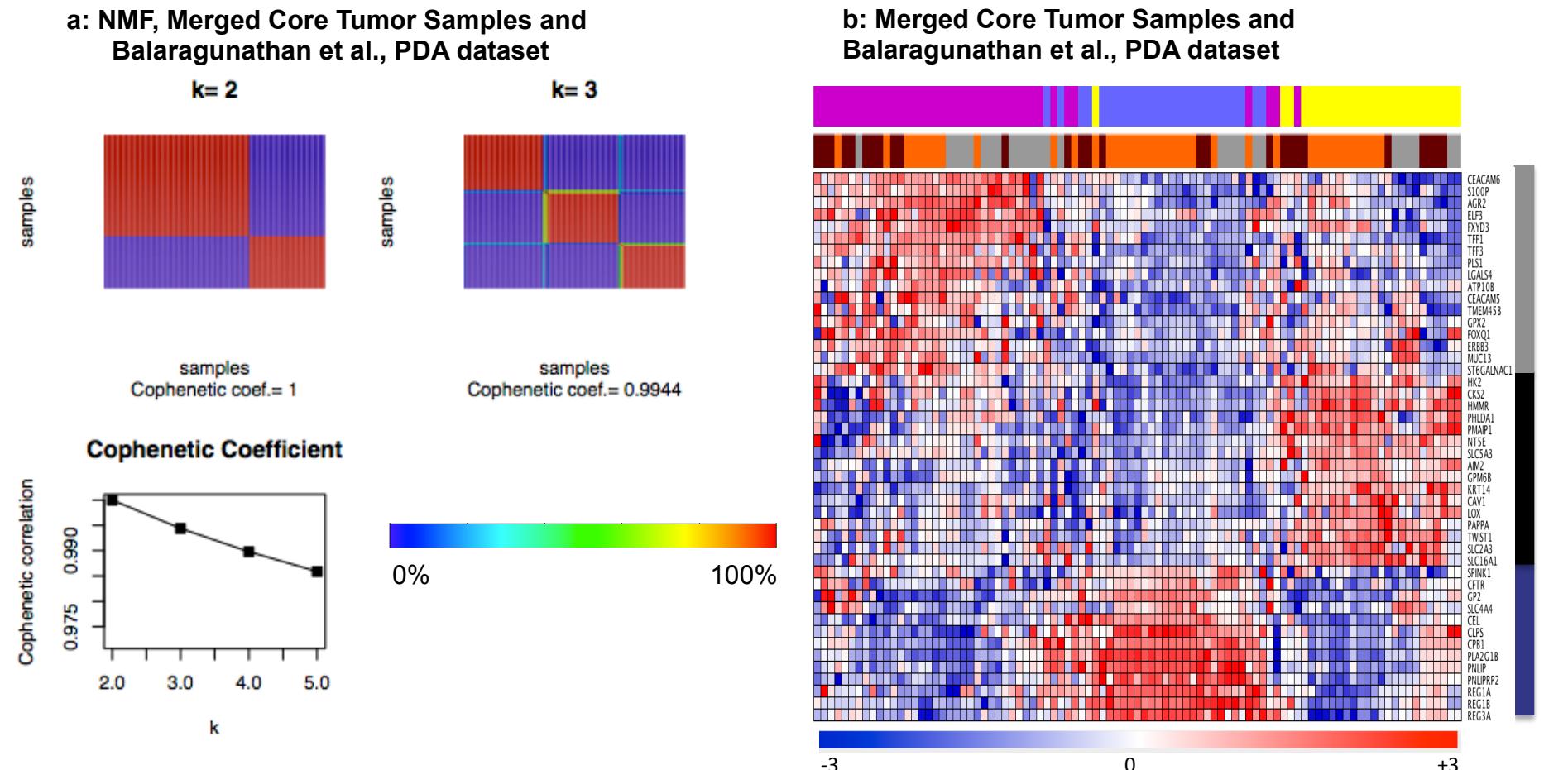
2e. Hierarchical clustering of mouse PDA cell lines with PDAssigner genes. The clusters show classical and QM-PDA subtypes.

Supplementary Figure 3. Immunohistochemistry detection of exocrine-like markers in PDA subtypes



Immunohistochemistry of exocrine-like markers. Representative sections of *PDAssigner*-subtyped UCSF PDA tumors were stained with antibodies against either ELA3A (a,b) or CFTR (3c,d). Non-exocrine-like samples (panels 3a,c) expressed relatively lower levels of these markers than exocrine-like samples (panels 3b,d), in agreement with gene expression profiling.

Supplementary Figure 4. PDA subtypes in additional microarray datasets

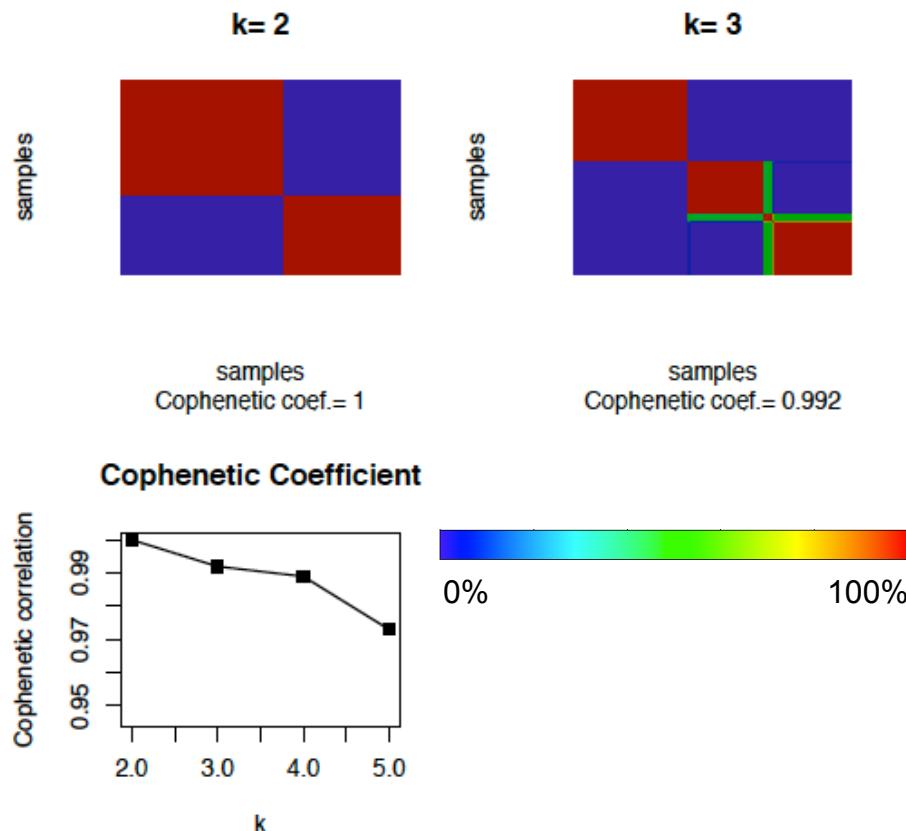


Confirmation of PDA Subtypes using on a unique microarray platform. a. NMF consensus matrix and cophenetic plot for $k = 2$ and 3 and **b.** Heatmap showing three subtypes of PDA in DWD-merged core clinical and Balaragunathan et al. (GSE11838) PDA microarray datasets using the *PDAAssigner* geneset. Balaragunathan et al. is a whole tumor Agilent Human 1A oligonucleotide microarray dataset. Samples from each dataset are found across all of the subtypes. The side bar denotes subtype specific genes in the *PDAAssigner*, with dark blue labeling exocrine-like genes, black labeling QM-PDA genes and gray labeling classical subtype genes.

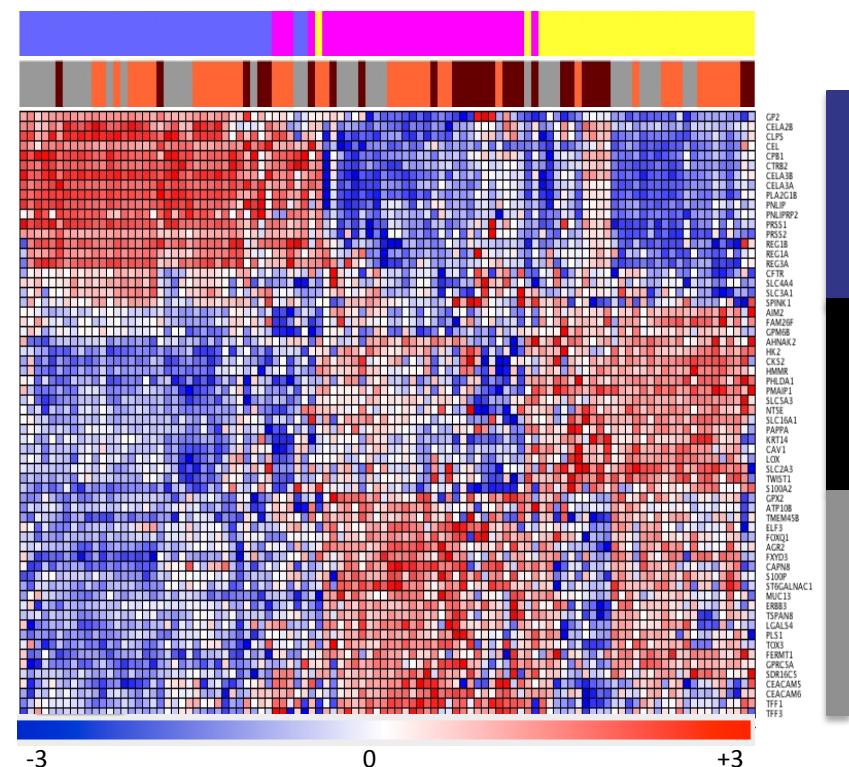
- █ Classical
- █ QM-PDA
- █ Exocrine-like
- █ UCSF
- █ Badea et al.
- █ Balaragunathan et al.

Supplementary Figure 4

c: NMF, Merged Core Tumor Samples and Pei et al., PDA dataset



d: Merged Core Tumor Samples and Pei et al., PDA dataset

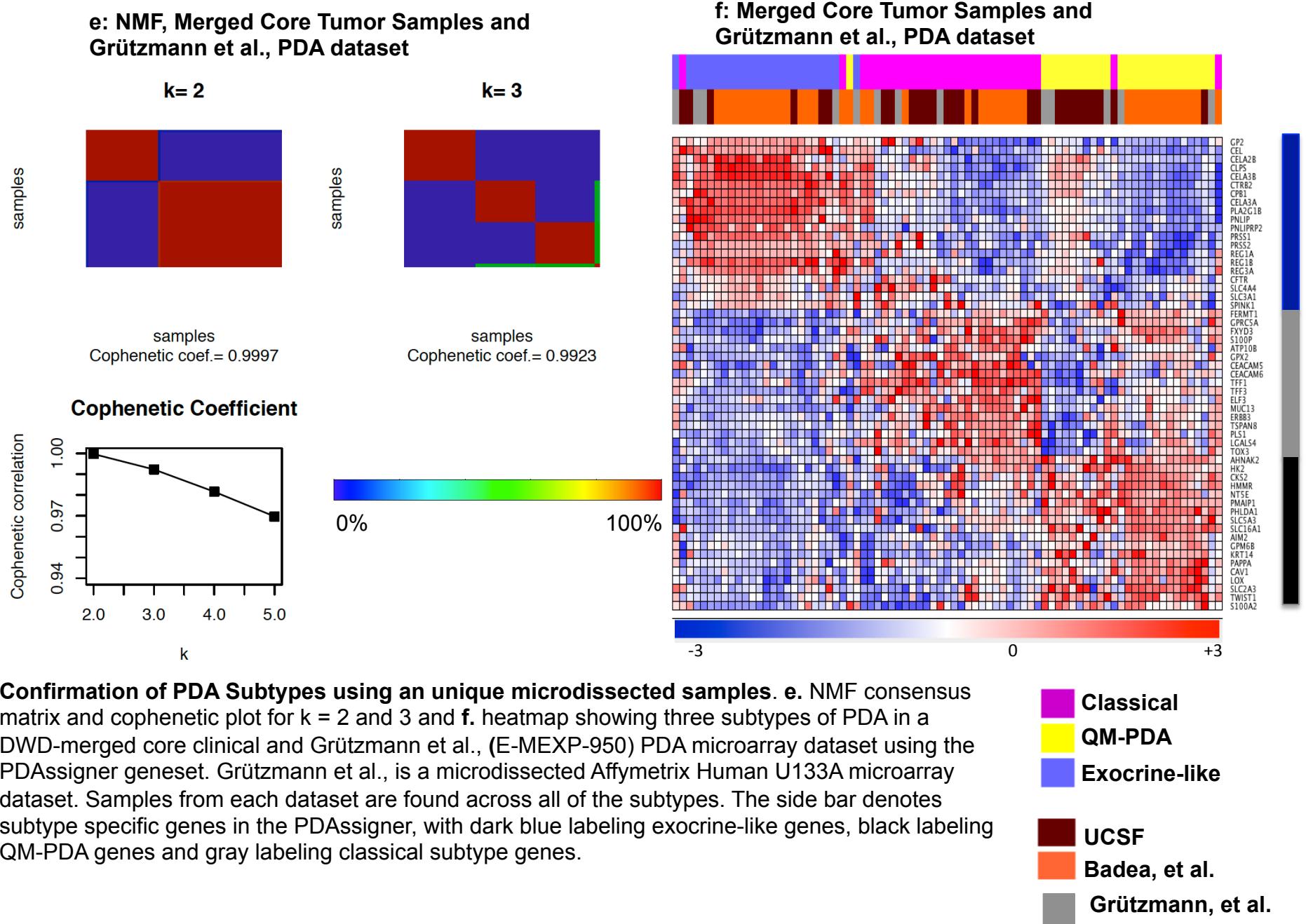


Confirmation of PDA Subtypes using an independent dataset. **c.** NMF consensus matrix and cophenetic plot for $k = 2$ and 3 and **d.** heatmap showing three subtypes of PDA in a DWD-merged core clinical and Pei et al., (GSE16515) PDA microarray dataset using the *PDAssigner* geneset. Pei et al., is a whole tumor Affymetrix Human U133plus2 microarray dataset. Samples from each dataset are found across all of the subtypes. The side bar denotes subtype specific genes in the *PDAssigner*, with dark blue labeling exocrine-like genes, black labeling QM-PDA genes and gray labeling classical subtype genes.

Classical
QM-PDA
Exocrine-like

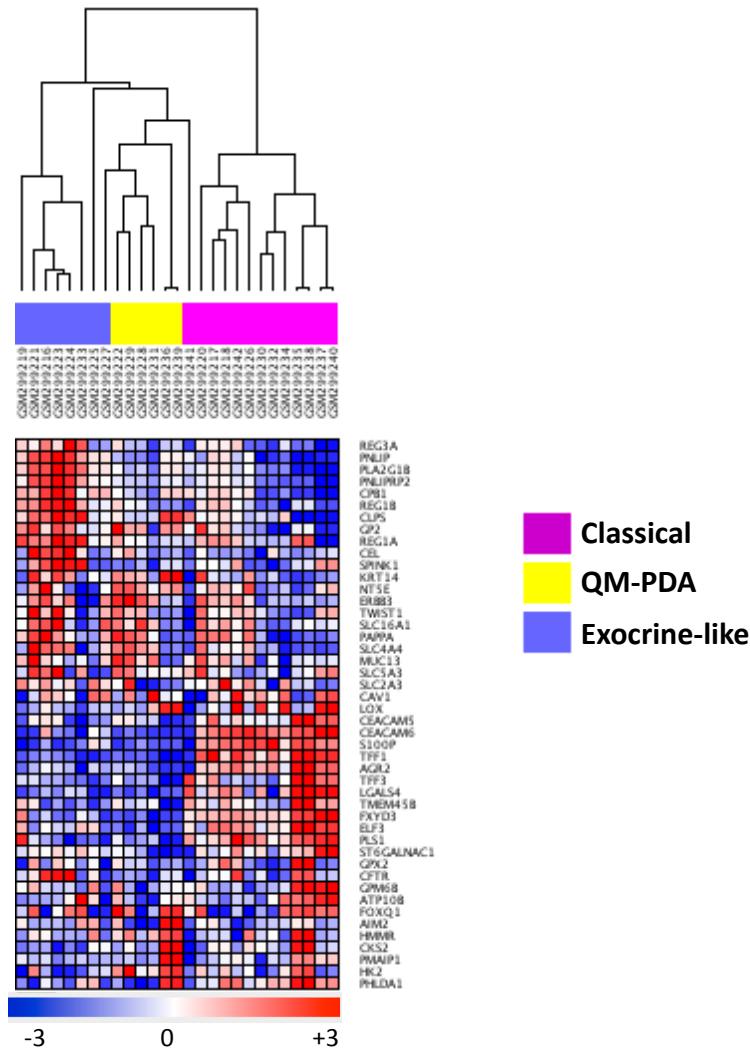
UCSF
Badea et al.
Pei et al.

Supplementary Figure 4

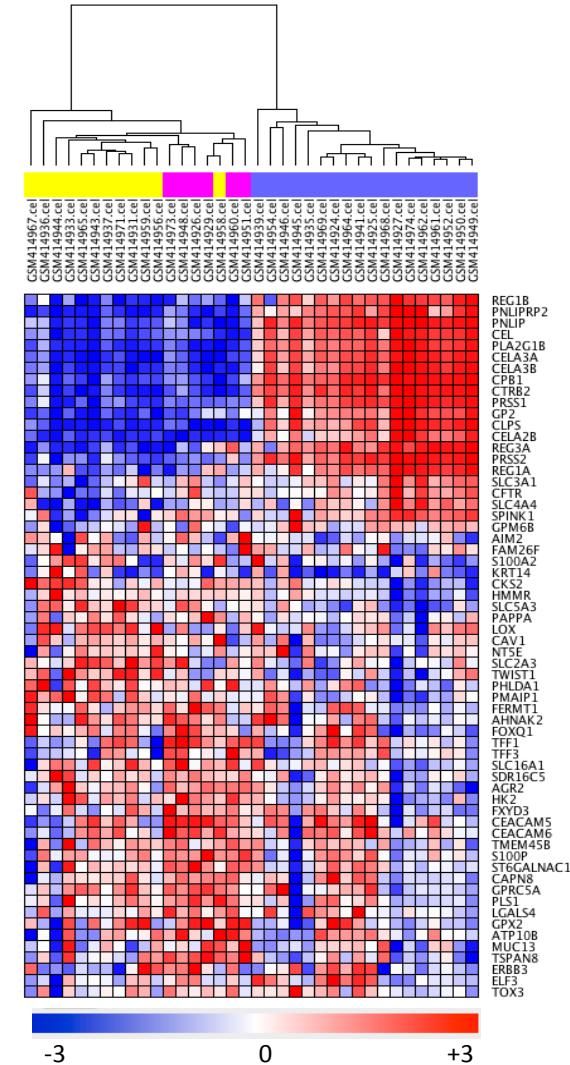


Supplementary Figure 4

g: PDAssigner Genes from Balaragunathan et al., PDA dataset



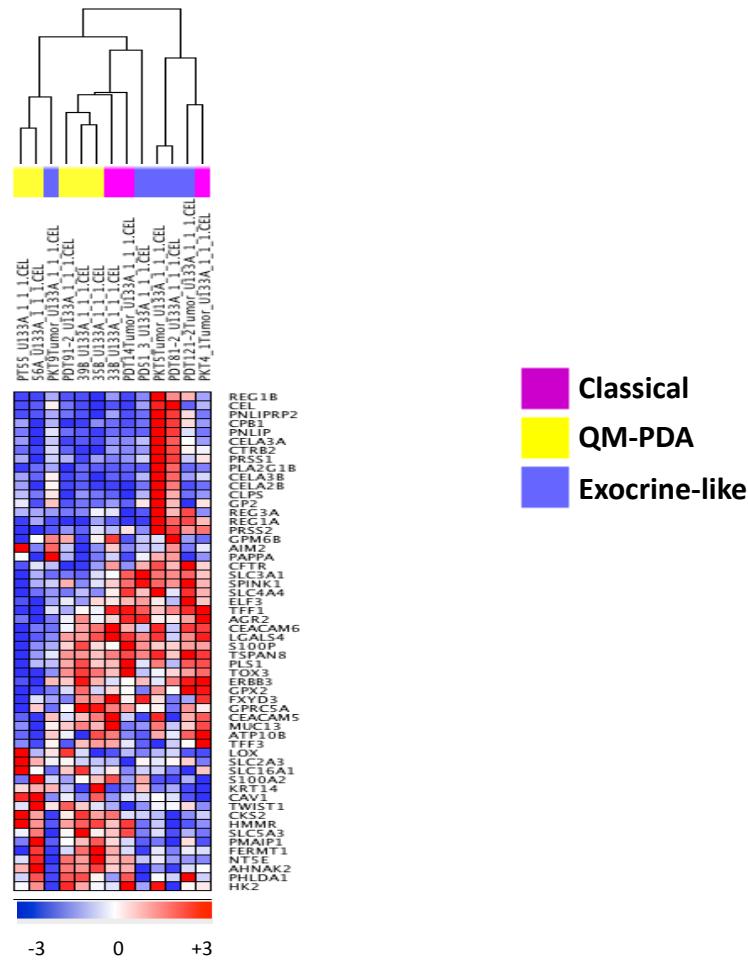
h: PDAssigner Genes from Pei et al., PDA dataset



Hierarchical clustering of **g.** Balaragunathan et al., and **h.** Pei et al., human PDA (public datasets) using PDAssigner genes. The clusters show classical, QM-PDA and exocrine-like subtypes.

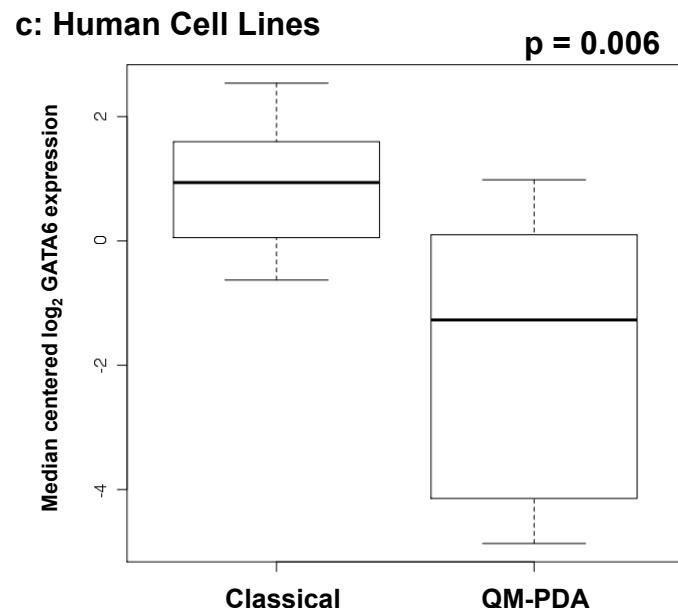
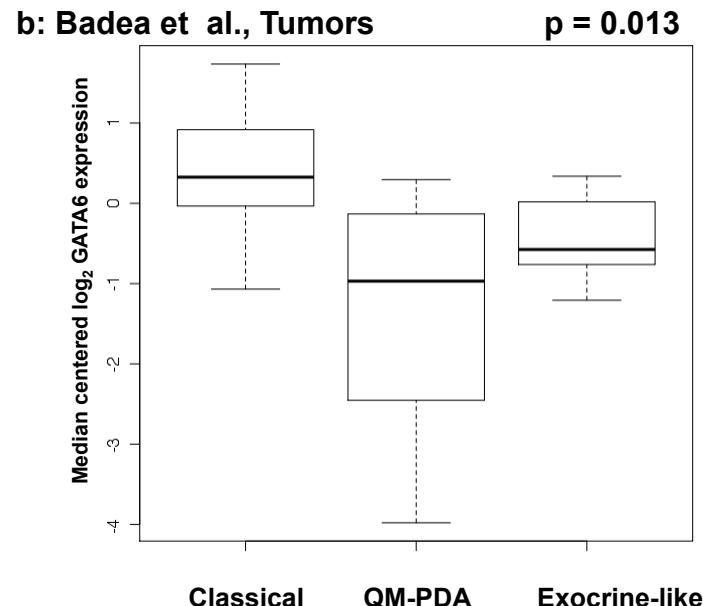
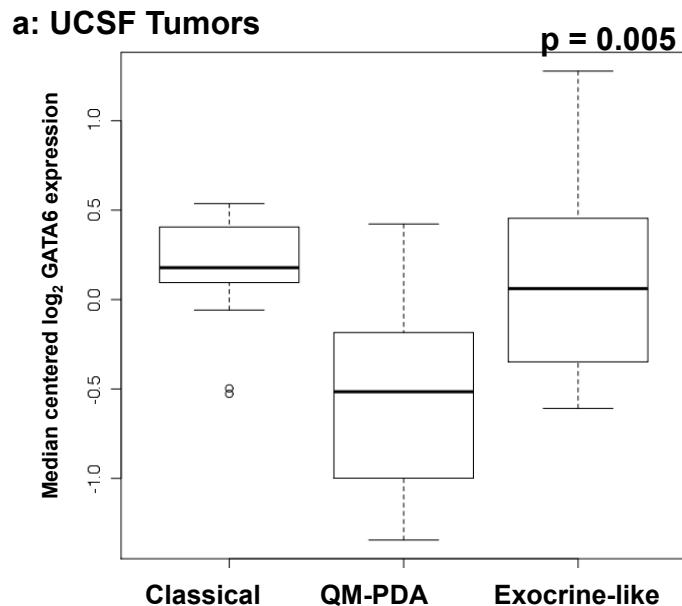
Supplementary Figure 4

i: PDAssigner Genes from Grützmann, et al. PDA dataset



i. Hierarchical clustering of Grützmann, et al., human PDA (public dataset) using PDAssigner genes. The clusters show classical, QM-PDA and exocrine-like subtypes.

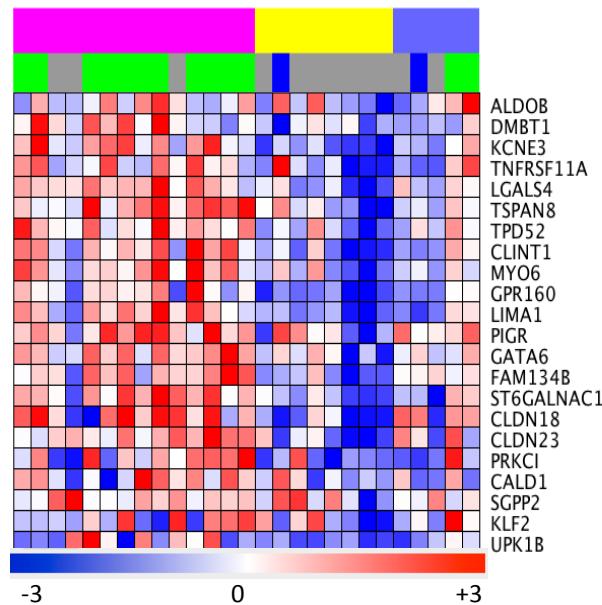
Supplementary Figure 5. GATA6 mRNA expression by subtype in:



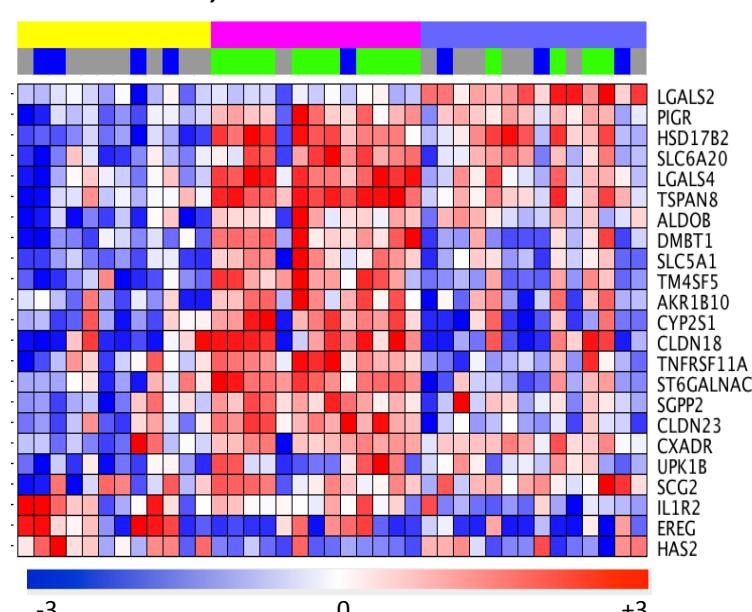
Association of GATA6 mRNA levels with subtypes in patient pancreatic tumors and cell lines. There was significantly higher expression of GATA6 in the classical subtype compared to QM-PDA and/or exocrine-like subtypes in: **a.** UCSF clinical PDA samples, **b.** Badea et al. PDA clinical samples, and **c.** human cell lines. The p-values were estimated using a Kruskal-Wallis Test.

Supplementary Figure 5. GATA6 Signature projected on:

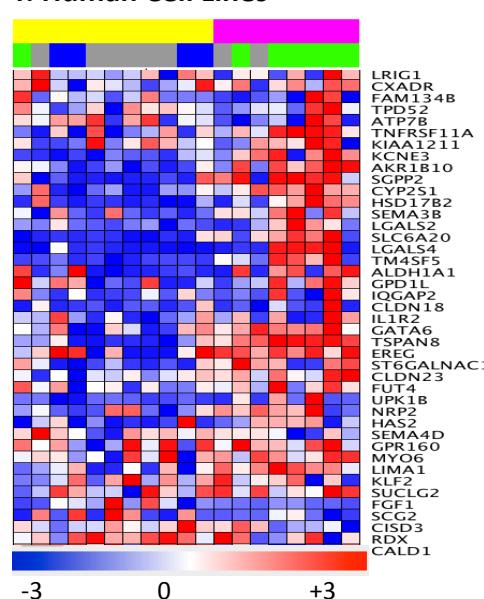
d: UCSF Tumors



e: Badea et al., Tumors



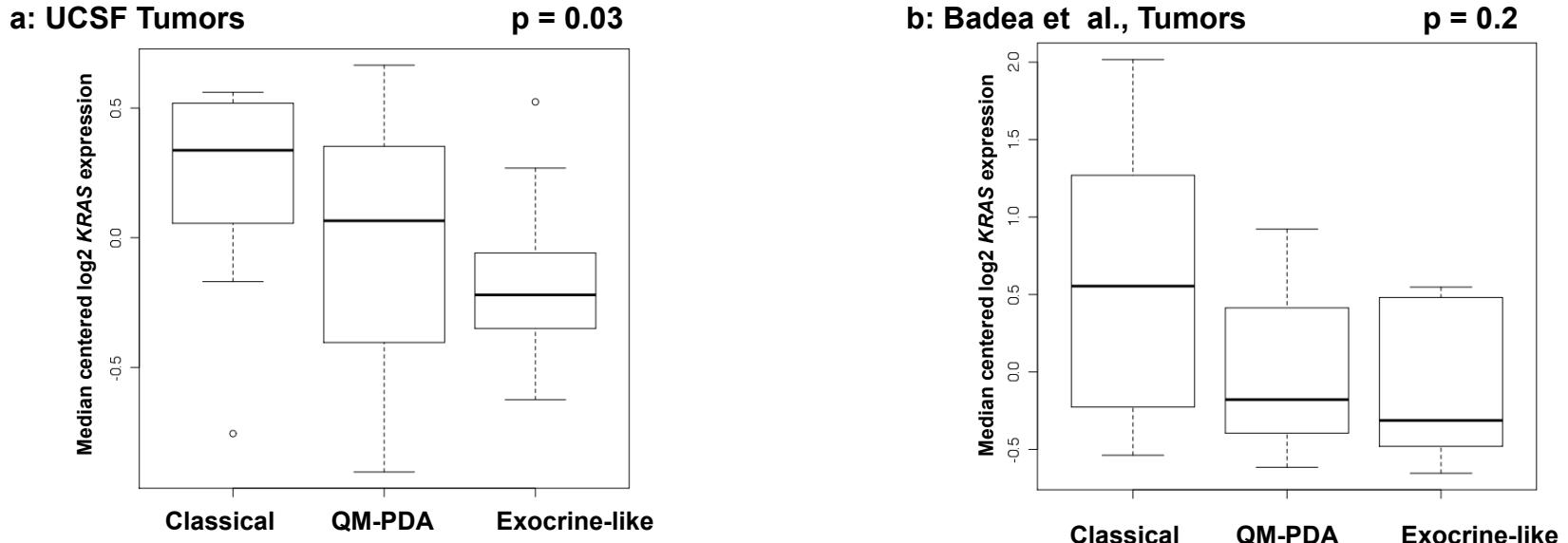
f: Human Cell Lines



Classical	█ Positive GATA6 signature FDR < 0.2
QM-PDA	█ Unknown, FDR > 0.2
Exocrine-like	█ Negative GATA6 signature FDR < 0.2

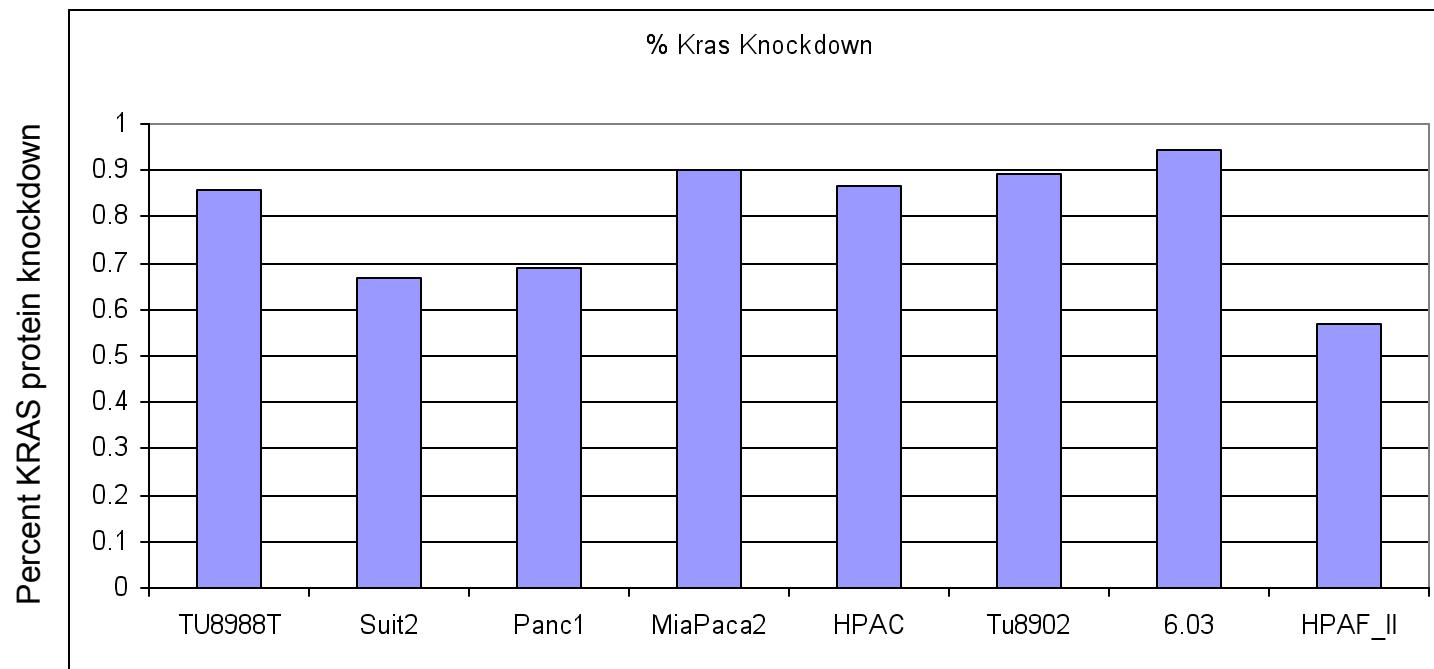
Association of GATA6 gene signature with PDA subtypes. The GATA6 gene expression signature (Kwei et al.) distinguishes samples with high or low GATA6 expression and was used for clustering the: **d.** UCSF clinical PDA samples, **e.** Badea et al. clinical PDA samples and **f.** human PDA cell lines. The samples significantly (FDR < 0.2) enriched for upregulated genes from Kwei et al. [as predicted by the NearestTemplatePrediction (NTP) algorithm] are denoted with a green top bar and those significantly enriched for downregulated genes with a blue top bar. Samples not enriched for either with a FDR > 0.2 are denoted with a grey bar. The PDA subtype sample assignments are shown in one of the top bars. Most of the genes overexpressed in GATA6 overexpressing cells (per Kwei et al.) were highly expressed in the classical subtype relative to the QM-PDA subtype.

Supplementary Figure 6: KRAS mRNA expression by subtype in:



Association of KRAS mRNA levels with PDA subtype. Classical subtype expresses relatively higher levels of KRAS than the QM-PDA or exocrine-like subtypes. **a.** UCSF clinical PDA samples and **b.** Badea et al. PDA clinical samples. p-values estimated by Kruskal Wallis Test.

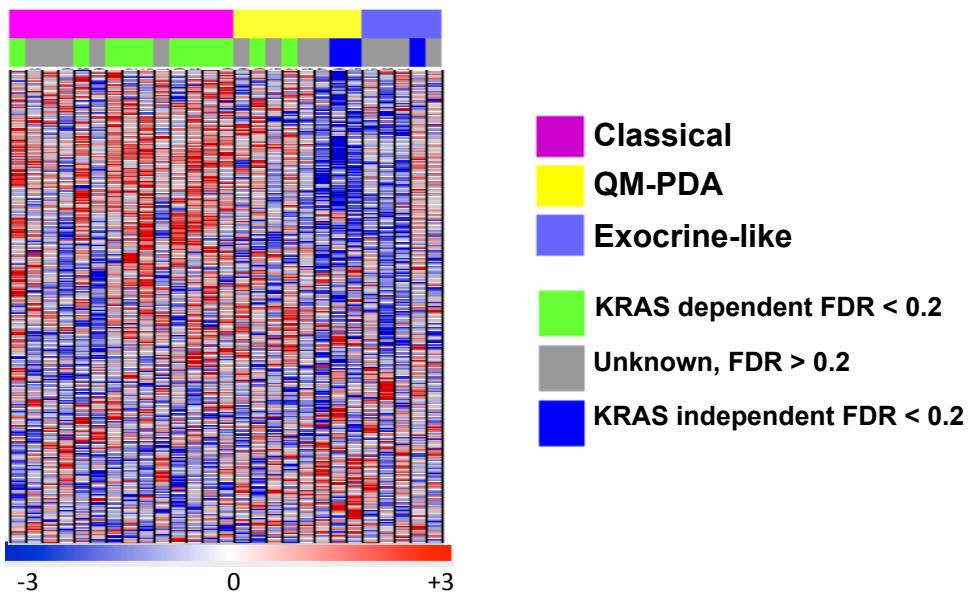
Supplementary Figure 6c. KRAS protein expression at the time of plating for relative proliferation:1-(shKRAS #5/shControl)



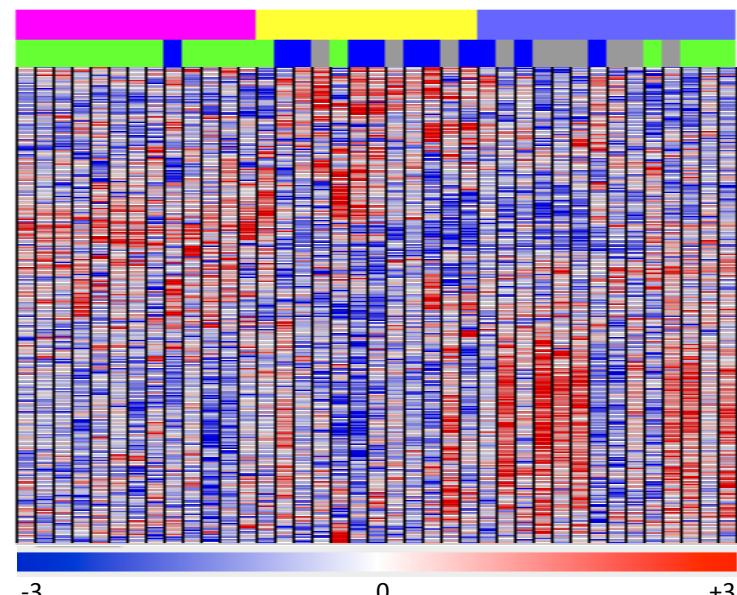
c. Percentage of KRAS protein knockdown by shRNA against *KRAS* in human PDA cell lines from figure 3. Knockdown was in general 70-90% as measured by Western Blot.

Supplementary Figure 7. KRAS dependency signature projected on:

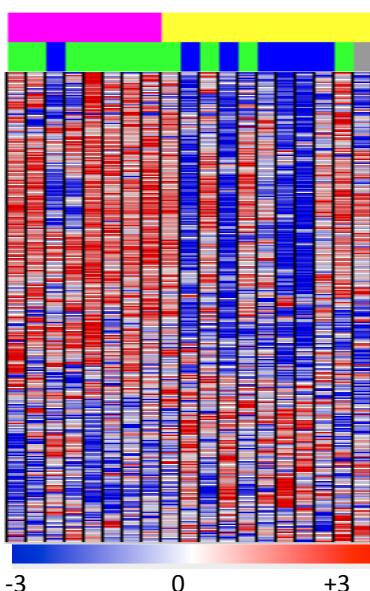
a: UCSF Tumors



b: Badea et al. Tumors



c: Human Cell Lines



A signature of KRAS addiction is enriched in the classical PDA subtype. Gene signature from Singh et al. projected on a: UCSF PDA tumors, b: Badea et al. tumors and c: Human PDA cell lines. The NTP algorithm was used to predict the Singh et al. defined KRAS-dependence of each sample with FDR < 0.2. The samples enriched for upregulated genes from KRAS dependency signature are KRAS dependent (green top bar) and those enriched for downregulated genes are KRAS independent (blue top bar). Whereas those that are not enriched for up or downregulated genes with FDR > 0.2 are called as unknown (grey top bar). The PDA subtype assignments of the samples are shown in one of the top bars.